Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Biomedical intelligence | Published 28 April 2016, doi:10.4414/smw.2016.14303

Cite this as: Swiss Med Wkly. 2016;146:w14303

Advanced ECG in 2016: is there more than just a tracing?

Tobias Reichlin[a,b], Roger Abächerli[b,c], Raphael Twerenbold[a,b], Michael Kühne[a,b], Beat Schaer[a,b], Christian Mueller[a,b], Christian Sticherling[a,b], Stefan Osswald[a,b]

[a] Division of Cardiology, University Hospital Basel, Switzerland

[b] Cardiovascular Research Institute Basel, University Hospital Basel, Switzerland

[c] Research, Schiller AG, Baar, Switzerland

Summary

The 12-lead electrocardiogram (ECG) is the most frequently used technology in clinical cardiology. It is critical for evidence-based management of patients with most cardiovascular conditions, including patients with acute myocardial infarction, suspected chronic cardiac ischaemia, cardiac arrhythmias, heart failure and implantable cardiac devices. In contrast to many other techniques in cardiology, the ECG is simple, small, mobile, universally available and cheap, and therefore particularly attractive. Standard ECG interpretation mainly relies on direct visual assessment.

The progress in biomedical computing and signal processing, and the available computational power offer fascinating new options for ECG analysis relevant to all fields of cardiology. Several digital ECG markers and advanced ECG technologies have shown promise in preliminary studies. This article reviews promising novel surface ECG technologies in three different fields. (1) For the detection of myocardial ischaemia and infarction, QRS morphology feature analysis, the analysis of high frequency QRS components (HF-QRS) and methods using vectorcardiography as well as ECG imaging are discussed. (2) For the identification and management of patients with cardiac arrhythmias, methods of advanced P-wave analysis are discussed and the concept of ECG imaging for noninvasive localisation of cardiac arrhythmias is presented. (3) For risk stratification of sudden cardiac death and the selection of patients for medical device therapy, several novel markers including an automated QRS-score for scar quantification, the QRS-T angle or the T-wave peak-to-end-interval are discussed.

Despite the existing preliminary data, none of the advanced ECG markers and technologies has yet accomplished the transition into clinical practice. Further refinement of these technologies and broader validation in large unselected patient cohorts are the critical next step needed to facilitate translation of advanced ECG technologies into clinical cardiology.

Key words: *advanced ECG; digital ECG marker; ECG imaging*

Introduction

It is more than a century ago that Willem Einthoven introduced the string galvanometer [1] and it was in 1924 that he was awarded the Nobel Prize for medicine or physiology for his invention [2]. The 12-lead electrocardiogram (ECG) has since become the most frequently performed cardiovascular test and approximately 200 million ECGs are recorded worldwide each year. It is an essential diagnostic tool in clinical cardiology and critical for evidence-based management of patients with most cardiovascular conditions including patients with acute myocardial infarction, suspected chronic cardiac ischaemia, cardiac arrhythmias, heart failure and implantable cardiac devices. In contrast to many other techniques in cardiology, the ECG is simple, small, mobile, universally available and cheap, all of which make the ECG a particularly attractive diagnostic method.

The progress in biomedical computing and signal processing, and the available computational power of microcontrollers and processors offer fascinating new options for ECG analysis, including improved filtering effects, morphology feature analysis [3], frequency content analysis [4], vectorcardiography analysis [5] and ECG imaging [6]. Regardless, the look of the standard 12-lead ECG has remained the same and the interpretation still relies mainly on direct visual assessment. The criteria for ECG interpretation have hardly changed over the past 25 years [7–11]. Using these conventional criteria, relevant limitations of the ECG leave, however, significant unmet clinical needs in various field of cardiology.

Even though no digital 12-lead ECG marker has made the transition into clinical cardiology yet, some advanced ECG markers and technologies have shown promise in small preliminary studies. Further refinement of these technologies and broader validation in large unselected patient cohorts are the critical next step needed to facilitate translation of these and other advanced ECG technologies into clinical cardiology. This article reviews promising novel surface ECG technologies for (1) detection of acute myocardial infarction (AMI) and ischaemia; (2) identification and management of patients with cardiac arrhythmias;

and (3) risk stratification for sudden cardiac death and selection of patients for medical device therapy.

Detection of acute myocardial infarction and ischaemia

Current role of the ECG in the detection of acute myocardial infarction

AMI is a major cause of death and disability worldwide. As highly effective treatments are available, early and accurate detection of AMI is crucial [12–14]. Clinical assessment, the 12-lead ECG and measurement of cardiac troponin form the three cornerstones of the early diagnosis of AMI in the emergency department [14]. The particular importance of the ECG is its pivotal role in identifying patients with complete occlusions of large epicardial vessels. A complete vascular occlusion results in transmural ischaemia, the maximal grade of ischaemia, which is reflected by *ST-elevation.* This subgroup of patients with so-called ST-elevation myocardial infarction (STEMI) is at highest risk for adverse events and needs immediate reperfusion therapy [15]. However, only a minority of AMI patients presents with transmural ischaemia and ST-elevation, whereas the majority of AMI patients has only nontransmural ischaemia, which result in either ST-depression, T-wave inversion or no ECG change at all. This group of AMI patients with nontransmural ischaemia and without ST-elevation are summarised as having non-ST-elevation myocardial infarction (NSTEMI).

Whereas major advances in the early identification of NSTEMI patients have recently been achieved by the development of more sensitive cardiac troponin assays [16–25], progress in the analysis and interpretation of the 12-lead ECG has been very limited over years and the criteria applied have remained virtually unchanged for more than a decade, focusing on ST-depression and T-wave inversion [14]. On the basis of these current ECG criteria, at least 25% of patients with AMI present with no diagnostic ECG abnormalities [18].

Current role of the ECG in the detection of myocardial ischaemia in the assessment of stable coronary artery disease

The incidence of coronary artery disease (CAD) eventually leading to AMI and severe heart failure is still increasing, mainly in emerging nations [26, 27]. The early detection of CAD and of exercise-induced myocardial ischaemia (as its pathophysiological hallmark) before the occurrence of a first AMI is one of the most important challenges in current cardiology [28–30]. For many years, exercise ECG testing has remained the most widely accessible and relatively inexpensive method for initial evaluation of suspected obstructive CAD and for assessment of its severity [31]. The ST-segment depression criteria recommended for detection of exercise-induced ischaemia have also been unchanged for years [32]. Clinical usefulness has, however, been limited by poor sensitivity of these standard criteria; almost 50% of patients with exercise-induced ischaemia have a false negative stress ECG, and this number is even higher in females [33, 34]. Hence, a large number of patients with suspected CAD require further investigation by imaging modalities including stress echocardiography, cardiac MRI or myocardial perfusion single photon emission tomography (MP-SPECT). In spite of being standard procedures in noninvasive detection of stress-induced myocardial ischaemia nowadays, all of them have several limitations, since they are mainly available in larger hospitals only, operator dependent, expensive, time consuming, and bound to radiotracer exposure in case of SPECT. Therefore, there is an unmet clinical and economical need for an easily applicable and cost-effective method to rule-in or rule-out stress-induced myocardial ischaemia [35].

Novel ECG markers assessing ventricular depolarisation for ischaemia detection

While the traditional criteria of ST-segment changes and T-wave changes focus on ventricular repolarisation, myocardial ischaemia also affects ventricular depolarisation, which occurs during the QRS complex (fig. 1)

However, quantification of QRS changes is more challenging than that of ST-segment changes because these changes are only subtle in many electrophysiological and anatomical situations. Several computationally generated ECG markers not recognisable by an observer's eye have been reported to occur during ischaemia, including amplitude changes of the R- and S-waves [3, 36] and changes in QRS slopes, angles and vectors [37, 38]. A more sophisticated approach focuses on high-frequency components within the QRS complex (HF-QRS) [4, 39]. Those HF-QRS components are very low in amplitude and are normally filtered out by conventional ECG devices. They originate from the fragmentation of the electrical activation wavefront caused by branching of the conduction system. In ischaemic regions, local slowing of conduction velocity reduces the wavefront fragmentation, causing changes in the intensity and morphology of HF-QRS signals [40]. Therefore, HF-QRS signals decrease in the presence of ischaemia. Recently, a high resolution exercise-ECG system that provides automated HF-QRS analysis has become commercially available. A recent pilot study reported that, with this system, HF-QRS analysis was more sensitive and more specific than ST-segment analysis to detect inducible ischaemia in patients undergoing MP-SPECT stress test [4]. Given that no standard values are established for HF-QRS or for the other novel ECG markers of depolarisa-

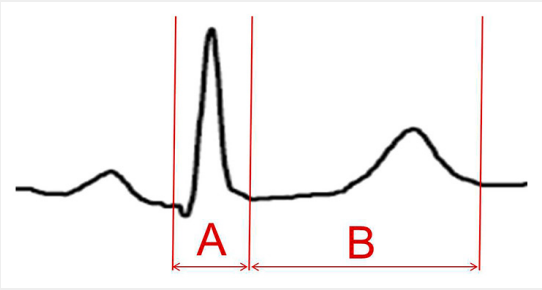

Figure 1

Normal sinus beat from lead II of a 12-lead ECG. Period (A) marks the ventricular depolarisation occurring during the QRS complex. Period (B) marks ventricular repolarisation consisting of the ST-segment and the T-wave.

tion, their application for now seems most feasible in patients undergoing exercise stress testing. The baseline ECG before the stress test in each patient may serve as its own "healthy" control for comparison with the ECG at maximal workload. Nevertheless, the algorithm detecting CAD was adapted to the case of ACS without any available baseline in the frame of a Swiss-Israeli collaboration funded by the European Union (Eurostars E!5495 HRQRS), the first results of which will be available soon.

Novel ECG markers assessing ventricular repolarisation for ischaemia detection

In addition to the traditional markers of ventricular repolarisation, i.e. ST-segment deviation and T-wave inversion, parameters from vectorcardiography quantifying ventricular repolarisation such as T-wave axis and T-loop morphology have been studied as potential markers of myocardial ischaemia. Myocardial ischaemia induced by coronary occlusion during cardiac revascularisation resulted in a significant change of T-wave axis as well as T-loop morphology [41]. Similarly, among unselected patients presenting with chest pain, an abnormal T-wave axis was more frequently found in patients with AMI than with other causes of chest pain [42].

ECG imaging for ischaemia detection

A limitation of current criteria is their focus on the presence of a threshold amount of ST-segment change. This necessarily leads to false positive and false negative diagnoses. Several groups have suggested methods for improving the accuracy of the 12-lead ECG and facilitating interpretation by using graphic tools to display the ECG-information on polar or Mercator maps [43–45]. However, all those methods rely on ST-segment deviation with all its inherent limitations.

One approach to overcoming some of the limitations of ST-deviations in the normal 12-lead ECG is to use higher-density electrode mapping to allow for better "ECG imaging". The clinical performance of such an 80-lead ECG system with 64 anterior and 16 posterior leads was assessed in a large study with 1830 unselected patients presenting with chest pain: using the additional leads, the rate of STEMI patients increased from 5.0% to 6.3% [46]. The system, however, is both difficult to apply and to interpret because of the large number of electrodes, and up to 10% of all ECGs had to be excluded from analysis owing to poor quality recordings [46].

More recently, a Canadian group has used high-density ECG data obtained from J-point measurements in 120 leads to calculate the unipolar epicardial surface potential map by use of the mathematical inverse solution method. Using the input of continuously reduced lead sets, it finally was possible to estimate the unipolar epicardial potential map using the information from the standard 12-lead ECG alone [47]. These epicardial potentials were then used to create a 17-segment polar map, which showed a good correspondence with simultaneously acquired MP-SPECT images in patients with acute ischaemia [48]. Furthermore, this method seemed to allow distinction between cardiac conditions with acute ischaemia and those with nonischaemic problems such as pericarditis or left ventricular hypertrophy (fig. 2) [49]. Even though this latter method in particular has shown potential in these small pilot studies, nothing is known about its value for identification of NSTEMI patients and validation in larger cohorts of unselected chest pain patients is needed.

Novel ECG technologies for identification and management of patients with arrhythmias

Current role of the ECG in the identification and management of patients with arrhythmias

The 12-lead ECG is the most important technology for diagnosis and management of patients with cardiac arrhythmias [50–52]. It allows the diagnosis of the ongoing arrhythmia and in, most cases, also a crude localisation of the arrhythmia origin. It assists in the selection of the appropriate treatment strategy for the individual patient, including the selection of patients suitable for catheter ablation therapy. Unmet clinical needs include the identification of patients with paroxysmal atrial fibrillation (AF) while in sinus rhythm, the prediction of success after catheter ablation in AF patients and a more accurate noninvasive localisation of arrhythmias, which could also be used to guide catheter ablation.

Is identification of patients with paroxysmal atrial fibrillation possible in sinus rhythm?

AF is the most commonly encountered cardiac arrhythmia. It is of particular medical and economic importance because of its association with embolic stroke. The identification of patients with paroxysmal AF is important to en-

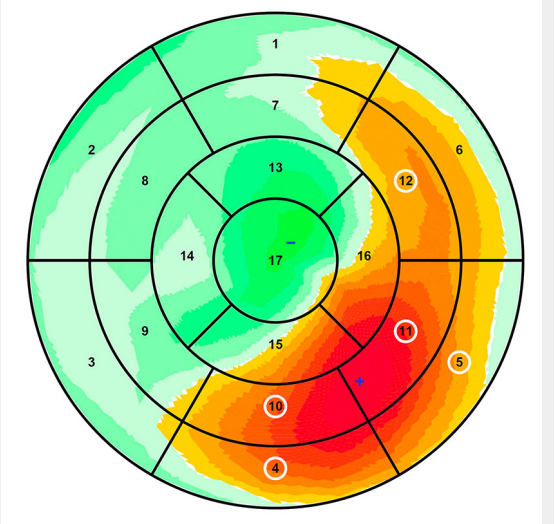

Figure 2

Polarmap of the unipolar epicardial surface potentials obtained at the J-point with ECG imaging in a patient with an left circumflex artery occlusion.

Epicardial unipolar potential distribution obtained from J-point measurements. Yellow to red areas indicate positive potentials and green areas indicate negative potentials. Following the American Heart Association standard 17 segment model, the central part of the image corresponds to the left-ventricular apex and the outermost segments correspond to the basal part of the left ventricular myocardium.

able stroke prevention by initiation of oral anticoagulation therapy [51]. Traditionally, patients are screened for subclinical paroxysmal AF by use of 24-hour Holter monitoring. This, however, has a limited diagnostic yield as a result of false negative results. Prolonged monitoring (using wearable or implantable loop recorders) is therefore more frequently used recently in clinical practice and has significantly increased the rate of AF detection [53, 54]. A reliable method to identify patients with or at increased risk for paroxysmal AF during sinus rhythm could remarkably improve management of patients with subclinical paroxysmal AF and has the potential to reduce embolic strokes.

Markers obtained from advanced P-wave analysis in the 12-lead ECG are of particular interest for this. The goal of these markers is to detect subclinical atrial remodelling, the morphological substrate for AF, and they therefore can be found in patients with or at risk for AF [55]. Markers that have been associated with AF in large longitudinal cohort studies are a prolonged P-wave duration >120 ms, P-wave dispersion >58 ms (difference between the widest and the narrowest P-wave in a 10 sec ECG), abnormal P-wave axis and increased P-wave area [56–59]. With currently available digital P-wave indices, however, the odds ratio rarely exceeds a value of 2 [56–58]. Additional markers with better discrimination are needed before they can be clinically applied.

Recent evidence suggests that left atrial abnormalities may be responsible for cardioembolic stroke even in the absence of detectable AF [60] or without a temporal relationship to AF episodes [61]. Accordingly, it is conceivable that anticoagulation therapy might be beneficial for patients with significant left atrial abnormalities in the absence (or before the occurrence) of AF. If so, the above P-wave markers indicating left atrial abnormalities would be perfectly suited for patient screening.

Prediction of success after catheter ablation in atrial fibrillation patients

Over the past 15 years, catheter ablation of AF has become a well-established and widely performed minimally invasive interventional therapy for many symptomatic AF patients [51, 62]. However, long-term AF recurrence rates are still up to 50% after single procedures. In addition to procedural limitations, a large extent of atrial remodelling is a key factor responsible for higher recurrence rates [63] Hence preprocedural assessment of the extent of atrial remodelling is critical for appropriate patient selection in order to maximise success after catheter ablation. While left atrial diameter and volume obtained by echocardiography are most commonly used to do so, advanced markers of P-wave analysis are an even more easily accessible way to quantify atrial remodelling. Indeed, P-wave duration, P-wave dispersion and P-wave terminal force in lead V1 have been found to be predictors of recurrence after catheter ablation in patients with paroxysmal AF [64, 65]. However, in most studies, the predictive value of the P-wave markers was not independent from those obtained with echocardiography. For now, imaging modalities remain the standard to assess atrial remodelling, but ongoing research might identify better, independent ECG markers to be used in patient selection for catheter ablation.

ECG mapping for noninvasive localisation of arrhythmias and to guide ablation procedures

Besides the diagnosis of an arrhythmia type and mechanism, the 12-lead ECG is also the standard technology for noninvasive localisation of arrhythmias, including localisation of accessory pathways in Wolff-Parkinson-White syndrome, of focal origins in atrial tachycardias or premature ventricular contractions (PVC) and of exit sites in ventricular tachycardias. However, the 12-lead ECG records the reflection of electrical activity on the surface of the body, not the heart itself. Accordingly, it has limited spatial resolution, the localisation information provided is often inaccurate and the mechanism of the arrhythmia reflected by its activation sequence cannot be assessed. A more accurate localisation of the arrhythmia origin therefore requires percutaneous transvascular point-by-point mapping, most often with the support of three-dimensional mapping systems. This technology however is invasive and time-consuming.

ECG mapping is a noninvasive method combining an ECG vest with >250 electrodes for high resolution recording of body surface electrical potentials with the detailed heart-torso anatomical geometry obtained from chest computed tomography. Using the electrical as well as the anatomical information, the local electrical signals over the entire epicardial surface of the entire heart can be calculated using the inverse solution method (fig. 3) [6].

The reliability of arrhythmia localisation by this novel method was compared head-to-head with the current standard invasive endocardial arrhythmia mapping technology using three-dimensional mapping systems. ECG mapping was able to localise the origin of a variety of arrhythmias including accessory pathways and PVCs as well as atrial

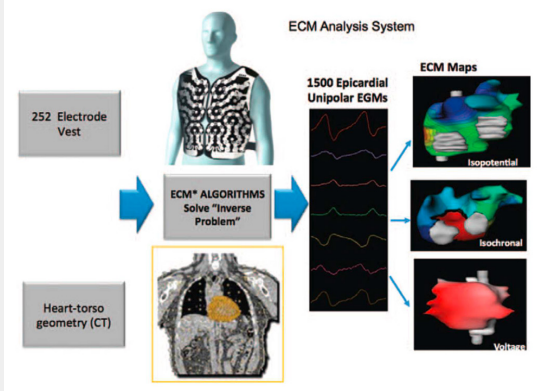

Figure 3

Overview of the components of the ECG mapping system. The key component of the mapping system is the 252 electrodes that are embedded in a vest that can easily be placed on a patient torso. With the vest on, a computed tomographic (CT) scan of the chest obtains the precise anatomical relation between the 252 electrodes on the vest and the epicardial surface of the heart. Once this anatomic relation is defined, 1500 unipolar electrograms can be calculated from the 252 electrodes using the inverse solution method. Next, isopotential, isochronal, and voltage maps can be reconstructed out of the 1500 unipolar electrograms. (Reproduced from Cakulev et al. [66] with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health. Please contact healthpermissions[at]wolterscluwer.com for further information.)

and ventricular tachycardias noninvasively with similar accuracy to the invasive mapping methods (fig. 4) [6, 66, 67]. In addition, ECG imaging has the advantage of identifying the tachycardia mechanism within just a few heart beats, because it provides simultaneous global activation mapping of the entire heart. The conventional invasive technology using sequential point-by-point mapping is much more time consuming and can be unsuccessful in a relevant proportion of patients because of the infrequent occurrence of the arrhythmia. Preliminary work has recently taken advantage of the global mapping property of ECG imaging in patients with persistent atrial fibrillation [68]. Using ECG imaging, the authors were able to identify driver domains in distinct areas of the right and left atrium the day before the ablation procedure. Targeting those predefined areas for ablation during the procedure, they were able to achieve AF termination with significantly less ablation compared with a control group (ablation time 28 vs 65 min) [68].

The novel technology of ECG imaging, however, still has relevant limitations. First, further clinical validation is needed, given that robust correlations of intracardiac mapping data with surface ECG mapping data during arrhythmias is rare. Among other problems, distinction of re-entrant mechanisms from focal mechanisms in the presence of delayed conduction is as yet unresolved. Second, the resolution for mapping of arrhythmias even from the high-voltage generating ventricles is in the range of 1–1.5 cm. The smaller atrial signals, particularly in diseased or ablated atria, further compromise resolution. Third, current systems are unstable in the sense that very small modifications of the original data result in multiple possible and highly erroneous solutions. Nevertheless, this novel and innovative approach certainly has the potential to improve remarkably the noninvasive localisation and characterisation of arrhythmias, to optimise the planning before catheter ablation, to shorten procedure duration and to improve procedural outcome.

Novel ECG technologies for risk stratification for sudden cardiac death in patients with heart failure, channelopathies or cardiomyopathies, and selection of patients for medical device therapy

Current role of the ECG in risk stratification for sudden cardiac death and selection of patients for medical device therapy

Sudden cardiac death (SCD) is the most feared consequence of almost all forms of heart disease. In Western countries, 50–100 sudden unexpected cardiac deaths occur per 100 000 population every year [69]. Ventricular tachycardia and ventricular fibrillation account for about half of the events. Risk stratification for SCD in patients with heart failure, channelopathies (such as Brugada syndrome or long QT syndrome) and cardiomyopathies (such as hypertrophic cardiomyopathy or arrythmogenic right ventricular cardiomyopathy) is important to optimise treatment and to allocate medical resources. One particular challenge is the selection of candidates for implantable cardioverter defibrillator (ICD) therapy for primary prevention of SCD.

From studies performed over the past two decades, it was learned that ICDs can prevent SCD in many forms of heart diseases [70, 71]. Current guidelines recommend ICD implantation for primary prevention of SCD in patients with heart failure and a left ventricular ejection fraction ≤35% [72]. With regards to channelopathies and cardiomyopathies, the role of ICD implantation for primary prevention of SCD is much less clear. Taken together, current risk stratification is suboptimal: only a minority of patients receiving ICDs will receive appropriate shocks. Conversely, the majority of SCD events occur in patients with an LVEF >35%, most of whom, according to current guidelines, are not candidates for an ICD [73]. The 12-lead ECG is a simple and cheap test providing information associated with anatomical (presence and extent of myocardial scar) and electrophysiological (repolarisation heterogeneity) cardiac pathological features. While markers obtained from the Holter ECG, including heart rate turbulence or T-wave alternans, may play a role in patient selection for ICD therapies, the 12-lead ECG currently is hardly used clinically for risk stratification in heart failure patients.

In the subgroup of patients with heart failure and complete left bundle-branch block (LBBB), cardiac resynchronisation therapy (CRT) offers a benefit in terms of heart failure symptoms and mortality [74]. The 12-lead-ECG is recommended for selection of patients for CRT implantation [74]. However, with the criteria recommended by current guidelines [74], approximately one third of patients undergoing CRT implantation do not obtain a relevant clinical benefit (“nonresponse”). A better knowledge of the pathophysiological conditions of the underlying heart muscle

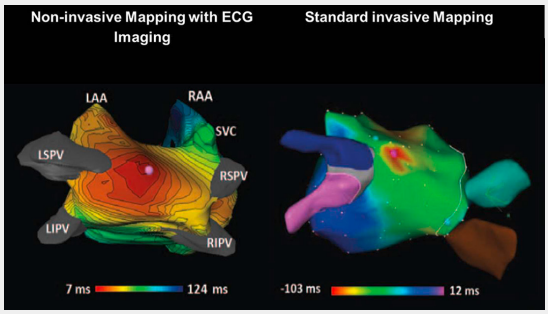

Figure 4

Maps obtained from ECG mapping and standard invasive mapping in a patient with incessant atrial tachycardia.
On the left side of the figure, the map obtained with ECG mapping demonstrated focal activation of the left atrium, with the earliest site of activation on the left atrial roof. On the right side of the figure, the CARTO map with the site of successful ablation that terminated the tachycardia. As can be appreciated, the ECG mapping technique successfully identified both the tachycardia mechanism as well as the site of earliest activation.
LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV =left superior pulmonary vein; RAA = right atrial appendage; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; SVC = superior vena cava

disease provided by the ECG might improve patient selection and reduce the proportion of nonresponders.

Novel ECG markers assessing ventricular depolarisation for risk stratification of SCD

The first 12-lead ECG marker of ventricular depolarisation assessed was the QRS duration (QRSd), which was found to correlate with cardiovascular mortality in the general population [75] as well as in patients with structural heart disease [76]. In order to detect and quantify myocardial scar with the 12-lead ECG, a manual QRS score was developed assessing 54 criteria and 10 leads, and assigning up to a maximum of 32 points for indicators of scarring, adjusted for conduction abnormalities (bundle branch-block patterns and LV hypertrophy), with each point corresponding to 3% of LV mass [77]. A good correlation between the estimated amount of LV scar based on the ECG QRS score and the amount of LV scar on cardiac MRI was found [78], which also makes the QRS score a marker of potential interest in assessing residual viability after myocardial infarction. Also, the QRS score correlated well with inducibility of VT during electrophysiological study [78] and with the occurrence of ICD shocks in primary prevention patients (hazard ratio for VT/VF events 0.5 in patients with a QRS score of 0) [79]. However, manual calculation of the QRS score takes up to 10 minutes per ECG, which precluded clinical application. An automated version of the QRS score was recently developed that adjusts for conduction abnormalities and measures all the 54 criteria automatically [80]. When using the automated QRS score to screen entire health system ECG databases, a QRS Score ≥5 was associated with an increase in mortality (odds ratio 2.33) [80]. The agreement between the manually adjudicated and the automated QRS score was high and the average absolute differences between the two scores was only 1.2 ± 1.5 points [81].

Another indicator of myocardial scar is fragmentation of the QRS complex (fQRS). Indeed, the presence of a fQRS was found both in postinfarct patients [82, 83] and in patients with nonischaemic cardiomyopathies [84]. The presence of fQRS was associated with an increase in mortality and arrhythmic events in stable CAD patients as well as in patients with ACS [84]. Limitations of the fQRS include its qualitative visual definition, which relies on the interpreters experience as well on the appropriate ECG filter settings. An automated quantitative measurement of fQRS therefore seems to be the next step needed in order to allow its use in clinical practice.

Novel ECG markers assessing ventricular repolarisation for risk stratification of SCD

Using the standard 12-lead ECG, research assessing repolarisation has primarily focused on markers reflecting repolarisation heterogeneity that are available from a single ECG beat. The simplest of these markers has been the QTc interval. Outside the inherited long-QT syndromes, a prolonged corrected QT interval was also predictive of sudden death in the general population [85], as well as in patients with CAD [86]. Based on data from SCD survivors, the early repolarisation pattern has been recognised as a potential risk marker for SCD [87]. This was confirmed in population-based epidemiological data, but the observed increase in risk was only 1.28, which seemed too small to be used in clinical practice at the moment [88]. The QRS-T-angle measured between the QRS-vector and the T-wave vector reflects depolarisation-repolarisation heterogeneity [89]. It was found to predict cardiac death in the general population [90], cardiac-related admissions and death in patients with chronic heart failure [91], and adverse events after AMI [92], with hazard ratios reaching up to 2 for patients with an abnormal QRS-T-angle. Given that the QRS-T-angle can be calculated easily in an automated fashion, it recently has been used successfully to screen entire health system ECG databases to identify patients at increased risk of death [80]. The dispersion of the QT-interval, measured as the difference between the shortest and the longest QT interval of all 12 leads, is another method to assess repolarisation heterogeneity. It was assessed as a marker for risk stratification in patients with chronic heart failure as well as in postmyocardial infarction patients [93, 94], but ultimately failed to be predictive in prospective studies [95]. The T-wave peak to T-wave end interval (Tpe) has more recently been shown to correlate with transmural as well as regional dispersion of repolarisation [96]. Clinically, the Tpe predicted SCD in the general population [97] as well as in patients with CAD [98], and appropriate ICD therapies in patients undergoing ICD implantation for primary prevention of SCD [99]. While the clinical value of individual markers has remained limited so far, it is conceivable that a combination of ECG risk markers will help to improve identification of patients at risk of SCD.

Novel ECG technologies to improve patient selection for cardiac resynchronisation therapy

While initial CRT studies included patients with prolonged QRS duration regardless of the underlying bundle-branch block morphology [100], subsequent subgroup analysis revealed that best results are seen in patients with LBBB and severe QRS prolongation of >150 ms [101, 102]. The QRS score as described above has been used to predict a favourable response to CRT. It was found that patients with a low estimated LV scar burden (QRS score 0–3) had a response rate of 78% compared with a response rate of only 45% in patients with a QRS score >9 [103]. The QRS score can therefore be used to identify a subgroup of severely sick patients with a large amount of LV scar who are unlikely to benefit from CRT despite the presence of LBBB. More recently, parameters from vectorcardiography have been used to predict a favourable response to CRT [5]. The three-dimensional area of the QRS complex, which combines QRS duration and electrical force of ventricular activation, performed best and predicted CRT response in LBBB patients better than QRS duration (area under the curve 0.78 vs 0.62, p = 0.03) [5]. And, finally, ECG imaging as described above has been used to study electrical dyssynchrony in patients undergoing CRT, who had LBBB or nonspecific intraventricular conduction disturbance (NICD) [104]. The noninvasive measurement of ventricular electronic uncoupling , and the difference between LV and RV activation time, predicted CRT response better than QRS duration or the presence of LBBB and, in particular identified all NICD patients who had a favourable response to CRT

[104]. This technology therefore might assist in the identification of potential CRT responders in the absence of LBBB.

Outlook

Despite the promising preliminary data presented, none of the advanced ECG markers and technologies has yet accomplished the transition into clinical practice. The reasons for this are twofold: with some of the markers, the added clinical benefit is only modest, while other markers lack sufficient clinical validation. A close and open collaboration between ECG engineers in academic institutions and the industry on the one side and clinical cardiologists on the other side is now critical to improve the novel technologies further. And adequate datasets from large clinical studies with digital ECG data available for analysis are needed for broader validation of the novel technologies in large unselected patient cohorts. Successful completion of the above two tasks has the potential to allow the transition of several advanced ECG markers and technologies into routine clinical practice, which could shift the role of the surface ECG in clinical cardiology as outlined in table 1.

Conclusions

The remarkable progress in biomedical computing, signal processing and computational power has generated novel ECG markers and technologies. These offer new opportunities to address current unmet needs in clinical cardiology in (1) the diagnosis of AMI and detection of myocardial ischaemia; (2) identification and management of patients with cardiac arrhythmias; and (3) risk stratification of sudden cardiac death and selection of patients for medical device therapy. Further refinement of these technologies and broader validation in large unselected patient cohorts are the next step needed to facilitate translation of advanced ECG technologies into clinical cardiology.

Disclosure statement: Dr. Reichlin has received research grants from the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the Goldschmidt-Jacobson-Foundation, the Professor Max Cloëtta Foundation, the University of Basel and the University Hospital Basel.
Dr. Abächerli is a part-time employee of Schiller AG. Dr. Twerenbold: none. Dr. Kühne: none. Dr. Schaer: none. Dr. Mueller: none. Dr. Sticherling: none. Dr. Osswald: none.
None of the authors has conflicts of interest with this article.

Correspondence: *PD Dr. Tobias Reichlin, MD, University Hospital Basel, Division of Cardiology, Petersgraben 4, CH-4031 Basel, tobias.reichlin[at]usb.ch*

References

1 Einthoven W, Jaffe AS, Venge P, Lindahl B. Galvanometrische registratie van het menschelijk electrocardiogram. In: Herinneringsbundel Professor S S Rosenstein Leiden, Netherlands: Eduard Ijdo 1902:101–7. Dutch.

2 Kligfield P. The centennial of the Einthoven electrocardiogram. J Electrocardiol. 2002;35(Suppl):123–9.

3 Surawicz B, Orr CM, Hermiller JB, Bell KD, Pinto RP. QRS changes during percutaneous transluminal coronary angioplasty and their possible mechanisms. J Am Coll Cardiol. 1997;30:452–8.

4 Sharir T, Merzon K, Kruchin I, et al. Use of electrocardiographic depolarization abnormalities for detection of stress-induced ischemia as defined by myocardial perfusion imaging. Am J Cardiol. 2012;109:642–50.

5 van Deursen CJ, Vernooy K, Dudink E, et al. Vectorcardiographic QRS area as a novel predictor of response to cardiac resynchronization therapy. J Electrocardiol. 2015;48:45–52.

6 Wang Y, Cuculich PS, Zhang J, et al. Noninvasive electroanatomic mapping of human ventricular arrhythmias with electrocardiographic imaging. Sci Transl Med. 2011;3:98ra84.

7 Hancock EW, Deal BJ, Mirvis DM, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part V: electrocardiogram changes associated with cardiac chamber hypertrophy: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:992–1002.

Table 1: Unmet clinical needs.

	Current role of surface ECG	Advanced ECG markers	Potential future role of surface ECG
Ischaemia			
Diagnosis of AMI	++	QRS morphology feature analysis High frequency QRS components Vectorcardiography ECG Imaging	+++
Detection of chronic ischaemia	+		+++
Cardiac arrhythmias			
Identification of AF pts in SR	–	Advanced P-wave analysis	+
Selection of AF pts for ablation	+		++
Noninvasive mapping of arrhythmias	+	ECG Imaging	+++
Heart Failure			
Risk stratification for SCD	–	QRS score, fragmentation of QRS, QRS-T Angle, QT dispersion, early repolarization pattern, T-wave peak to T-wave end interval	+
Patient selection for CRT	++	QRS score Vectorcardiography ECG Imaging	+++

ECG = electrocardiogram; AMI = acute myocardial infarction; AF = atrial fibrillation; SR = sinus rhythm; SCD = sudden cardiac death; CRT = cardiac resynchronisation therapy

8 Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2007;49:1109–27.

9 Mason JW, Hancock EW, Gettes LS, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part II: electrocardiography diagnostic statement list a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2007;49:1128–35.

10 Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:982–91.

11 Wagner GS, Macfarlane P, Wellens H, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:1003–11.

12 Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e663–828.

13 Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999–3054.

14 Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012;126:2020–35.

15 Task Force on the management of STseamiotESoC, Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569–619.

16 Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012;33:2252–7.

17 Safford MM, Parmar G, Barasch CS, et al. Hospital laboratory reporting may be a barrier to detection of "microsize" myocardial infarction in the US: an observational study. BMC Health Serv Res. 2013;13:162.

18 Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009;361:858–67.

19 Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med. 2009;361:868–77.

20 Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA. 2011;306:2684–93.

21 Reichlin T, Schindler C, Drexler B, et al. One-Hour Rule-out and Rule-in of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T. Arch Intern Med. 2012;172:1211–8.

22 Rubini Gimenez M, Twerenbold R, Reichlin T, et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. Eur Heart J. 2014 May 19. pii: ehu188. [Epub ahead of print].

23 Reiter M, Twerenbold R, Reichlin T, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J. 2011;32:1379–89.

24 Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation. 2011;124:136–45.

25 Haaf P, Drexler B, Reichlin T, et al. High-sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac noncoronary artery disease. Circulation. 2012;126:31–40.

26 Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe: epidemiological update. Eur Heart J. 2013;34:3028–34.

27 Reddy KS. Cardiovascular Disease in Non-Western Countries. N Engl J Med. 2004;350:2438–40.

28 Grech ED. Pathophysiology and investigation of coronary artery disease. BMJ. 2003;326:1027–30.

29 Greenland P, Gaziano JM. Clinical practice. Selecting asymptomatic patients for coronary computed tomography or electrocardiographic exercise testing. N Engl J Med. 2003;349:465–73.

30 Members TF, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34:2949–3003.

31 Kligfield P, Okin PM. Evolution of the exercise electrocardiogram. Am J Cardiol. 1994;73:1209–10.

32 Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128:873–934.

33 Task Force M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34:2949–3003.

34 Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation. 1989;80:87–98.

35 Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010;56:e50–e103.

36 Barnhill JE, 3rd, Tendera M, Cade H, Campbell WB, Smith RF. Depolarization changes early in the course of myocardial infarction: significance of changes in the terminal portion of the QRS complex. J Am Coll Cardiol. 1989;14:143–9.

37 Ringborn M, Romero D, Pueyo E, et al. Evaluation of depolarization changes during acute myocardial ischemia by analysis of QRS slopes. J Electrocardiol. 2011;44:416–24.

38 Romero D, Ringborn M, Laguna P, Pueyo E. Detection and quantification of acute myocardial ischemia by morphologic evaluation of QRS changes by an angle-based method. J Electrocardiol. 2013;46:204–14.

39 Pettersson J, Pahlm O, Carro E, et al. Changes in high-frequency QRS components are more sensitive than ST-segment deviation for detecting acute coronary artery occlusion. J Am Coll Cardiol. 2000;36:1827–34.

40 Abboud S, Berenfeld O, Sadeh D. Simulation of high-resolution QRS complex using a ventricular model with a fractal conduction system. Effects of ischemia on high-frequency QRS potentials. Circ Res. 1991;68:1751–60.

41 Rubulis A, Jensen J, Lundahl G, Tapanainen J, Wecke L, Bergfeldt L. T vector and loop characteristics in coronary artery disease and during acute ischemia. Heart Rhythm. 2004;1:317–25.

42 de Torbal A, Kors JA, van Herpen G, et al. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. Cardiology. 2004;101:199–207.

43 Bacharova L, Mateasik A, Carnicky J, et al. The Dipolar ElectroCARdioTOpographic (DECARTO)-like method for graphic presentation of location and extent of area at risk estimated from ST-segment deviations in patients with acute myocardial infarction. J Electrocardiol. 2009;42:172–80.

44 Strauss DG, Olson CW, Wu KC, et al. Vectorcardiogram synthesized from the 12-lead electrocardiogram to image ischemia. J Electrocardiol. 2009;42:190–7.

45 Andersen MP, Terkelsen CJ, Struijk JJ. The ST Compass: spatial visualization of ST-segment deviations and estimation of the ST injury vector. J Electrocardiol. 2009;42:181–9.

46 Hoekstra JW, O'Neill BJ, Pride YB, et al. Acute detection of ST-elevation myocardial infarction missed on standard 12-Lead ECG with a novel 80-lead real-time digital body surface map: primary results from the multicenter OCCULT MI trial. Ann Emerg Med. 2009;54:779–88 e1.

47 Horacek BM, Clements JC. The inverse problem of electrocardiography: a solution in terms of single- and double-layer sources of the epicardial surface. Math Biosci. 1997;144:119–54.

48 Horacek BM, Sapp JL, Penney CJ, Warren JW, Wang JJ. Comparison of epicardial potential maps derived from the 12-lead electrocardiograms with scintigraphic images during controlled myocardial ischemia. J Electrocardiol. 2011;44:707–12.

49 Akil S, Al-Mashat M, Heden B, et al. Discrimination of ST deviation caused by acute coronary occlusion from normal variants and other abnormal conditions, using computed electrocardiographic imaging based on 12-lead ECG. J Electrocardiol. 2013;46:197–203.

50 Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias – executive summary. a report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines (writing committee to develop guidelines for the management of patients with supraventricular arrhythmias) developed in collaboration with NASPE-Heart Rhythm Society. J Am Coll Cardiol. 2003;42:1493–531.

51 Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719–47.

52 Pedersen CT, Kay GN, Kalman J, et al. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. Europace. 2014;16:1257–83.

53 Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370:2467–77.

54 Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370:2478–86.

55 Platonov PG. P-wave morphology: underlying mechanisms and clinical implications. Ann Noninvasive Electrocardiol. 2012;17:161–9.

56 Magnani JW, Johnson VM, Sullivan LM, et al. P wave duration and risk of longitudinal atrial fibrillation in persons >/= 60 years old (from the Framingham Heart Study). Am J Cardiol. 2011;107:917–21 e1.

57 Magnani JW, Zhu L, Lopez F, et al. P-wave indices and atrial fibrillation: cross-cohort assessments from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2015;169:53–61 e1.

58 Perez MV, Dewey FE, Marcus R, et al. Electrocardiographic predictors of atrial fibrillation. Am Heart J. 2009;158:622–8.

59 Nielsen JB, Kuhl JT, Pietersen A, et al. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. Heart Rhythm. 2015;12:1887–95.

60 Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366:120–9.

61 Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. Heart Rhythm. 2011;8:1416–23.

62 Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659–66.

63 Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005;45:285–92.

64 Salah A, Zhou S, Liu Q, Yan H. P wave indices to predict atrial fibrillation recurrences post pulmonary vein isolation. Arq Bras Cardiol. 2013;101:519–27.

65 Caldwell J, Koppikar S, Barake W, et al. Prolonged P-wave duration is associated with atrial fibrillation recurrence after successful pulmonary vein isolation for paroxysmal atrial fibrillation. J Interv Card Electrophysiol. 2014;39:131–8.

66 Cakulev I, Sahadevan J, Arruda M, et al. Confirmation of novel noninvasive high-density electrocardiographic mapping with electrophysiology study: implications for therapy. Circ Arrhythm Electrophysiol. 2013;6:68–75.

67 Shah AJ, Hocini M, Xhaet O, et al. Validation of novel 3-dimensional electrocardiographic mapping of atrial tachycardias by invasive mapping and ablation: a multicenter study. J Am Coll Cardiol. 2013;62:889–97.

68 Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation. 2014;130:530–8.

69 Fishman GI, Chugh SS, Dimarco JP, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122:2335–48.

70 Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37.

71 Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877–83.

72 McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787–847.

73 Myerburg RJ, Reddy V, Castellanos A. Indications for implantable cardioverter-defibrillators based on evidence and judgment. J Am Coll Cardiol. 2009;54:747–63.

74 Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34:2281–329.

75 Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S, Froelicher VF. Prognostic Significance of Quantitative QRS Duration. Am J Med. 2006;119:600–6.

76 Kalahasti V, Nambi V, Martin DO, et al. QRS duration and prediction of mortality in patients undergoing risk stratification for ventricular arrhythmias. Am J Cardiol. 2003;92:798–803.

77 Strauss DG, Selvester RH. The QRS complex – a biomarker that "images" the heart: QRS scores to quantify myocardial scar in the presence of normal and abnormal ventricular conduction. J Electrocardiol. 2009;42:85–96.

78 Strauss DG, Selvester RH, Lima JA, et al. ECG quantification of myocardial scar in cardiomyopathy patients with or without conduction defects: correlation with cardiac magnetic resonance and arrhythmogenesis. Circ Arrhythm Electrophysiol. 2008;1:327–36.

79 Strauss DG, Poole JE, Wagner GS, et al. An ECG index of myocardial scar enhances prediction of defibrillator shocks: an analysis of the Sudden Cardiac Death in Heart Failure Trial. Heart Rhythm. 2011;8:38–45.

80 Strauss DG, Mewton N, Verrier RL, et al. Screening entire health system ECG databases to identify patients at increased risk of death. Circ Arrhythm Electrophysiol. 2013;6:1156–62.

81 Xia X, Wieslander B, Strauss DG, et al. Automatic QRS Selvester scoring system in patients with left bundle branch block. Europace. 2016;18:308–14 .

82 Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation. 2006;113:2495–501.

83 Das MK, Suradi H, Maskoun W, et al. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circ Arrhythm Electrophysiol. 2008;1:258–68.

84 Das MK, Zipes DP. Antiarrhythmic and nonantiarrhythmic drugs for sudden cardiac death prevention. J Cardiovasc Pharmacol. 2010;55:438–49.

85 Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol. 2006;47:362–7.

86 Chugh SS, Reinier K, Singh T, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. Circulation. 2009;119:663–70.

87 Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med. 2008;358:2016–23.

88 Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med. 2009;361:2529–37.

89 Geselowitz DB. The ventricular gradient revisited: relation to the area under the action potential. IEEE Trans Biomed Eng. 1983;30:76–7.

90 Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart Rhythm. 2005;2:73–8.

91 Gotsman I, Keren A, Hellman Y, Banker J, Lotan C, Zwas DR. Usefulness of electrocardiographic frontal QRS-T angle to predict increased morbidity and mortality in patients with chronic heart failure. Am J Cardiol. 2013;111:1452–9.

92 Zabel M, Acar B, Klingenheben T, Franz MR, Hohnloser SH, Malik M. Analysis of 12-lead T-wave morphology for risk stratification after myocardial infarction. Circulation 2000;102:1252-7.

93 Glancy JM, Garratt CJ, Woods KL, de Bono DP. QT dispersion and mortality after myocardial infarction. Lancet. 1995;345:945–8.

94 Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. Lancet. 1994;343:327–9.

95 Zabel M, Klingenheben T, Franz MR, Hohnloser SH. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction: results of a prospective, long-term follow-up study. Circulation. 1998;97:2543–50.

96 Opthof T, Coronel R, Janse MJ. Is there a significant transmural gradient in repolarization time in the intact heart?: Repolarization Gradients in the Intact Heart. Circ Arrhythm Electrophysiol. 2009;2:89–96.

97 Porthan K, Viitasalo M, Toivonen L, et al. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. Circ Arrhythm Electrophysiol. 2013;6:690–6.

98 Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol. 2011;4:441–7.

99 Rosenthal TM, Stahls PF, 3rd, Abi Samra FM, et al. T-peak to T-end interval for prediction of ventricular tachyarrhythmia and mortality in a primary prevention population with systolic cardiomyopathy. Heart Rhythm. 2015;12:1789–97.

100 Cleland JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013;34:3547–56.

101 Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med. 2011;171:1454–62.

102 Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J. 2012;163:260–7 e3.

103 Sweeney MO, van Bommel RJ, Schalij MJ, Borleffs CJ, Hellkamp AS, Bax JJ. Analysis of ventricular activation using surface electrocardiography to predict left ventricular reverse volumetric remodeling during cardiac resynchronization therapy. Circulation. 2010;121:626–34.

104 Ploux S, Lumens J, Whinnett Z, et al. Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: beyond QRS duration and left bundle branch block morphology. J Am Coll Cardiol. 2013;61:2435–43.

Figures (large format)

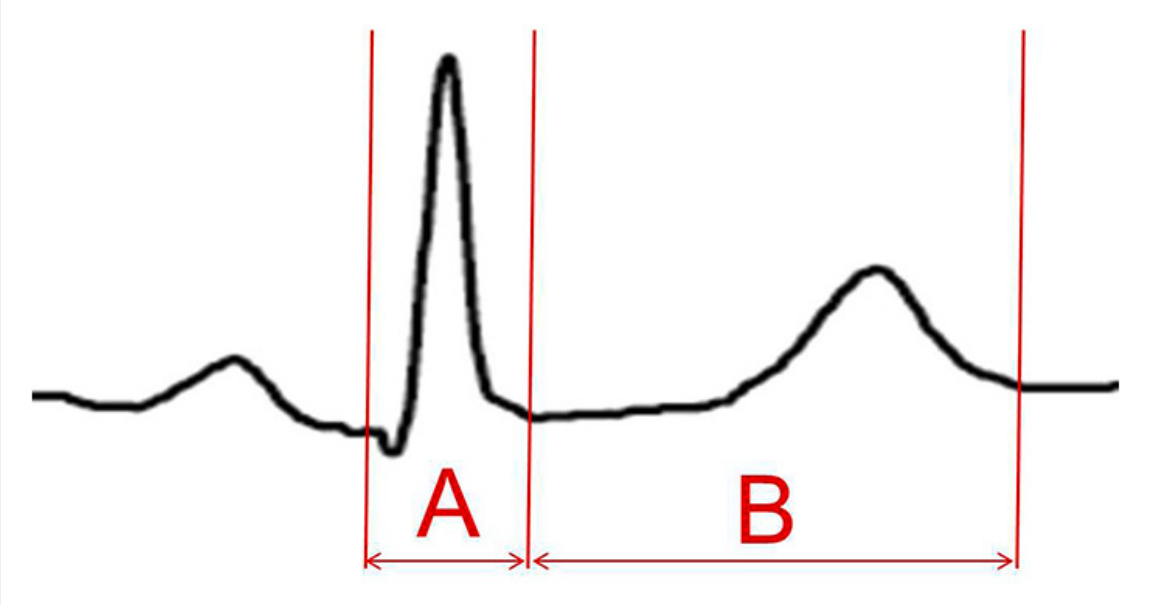

Figure 1

Normal sinus beat from lead II of a 12-lead ECG. Period (A) marks the ventricular depolarisation occurring during the QRS complex. Period (B) marks ventricular repolarisation consisting of the ST-segment and the T-wave.

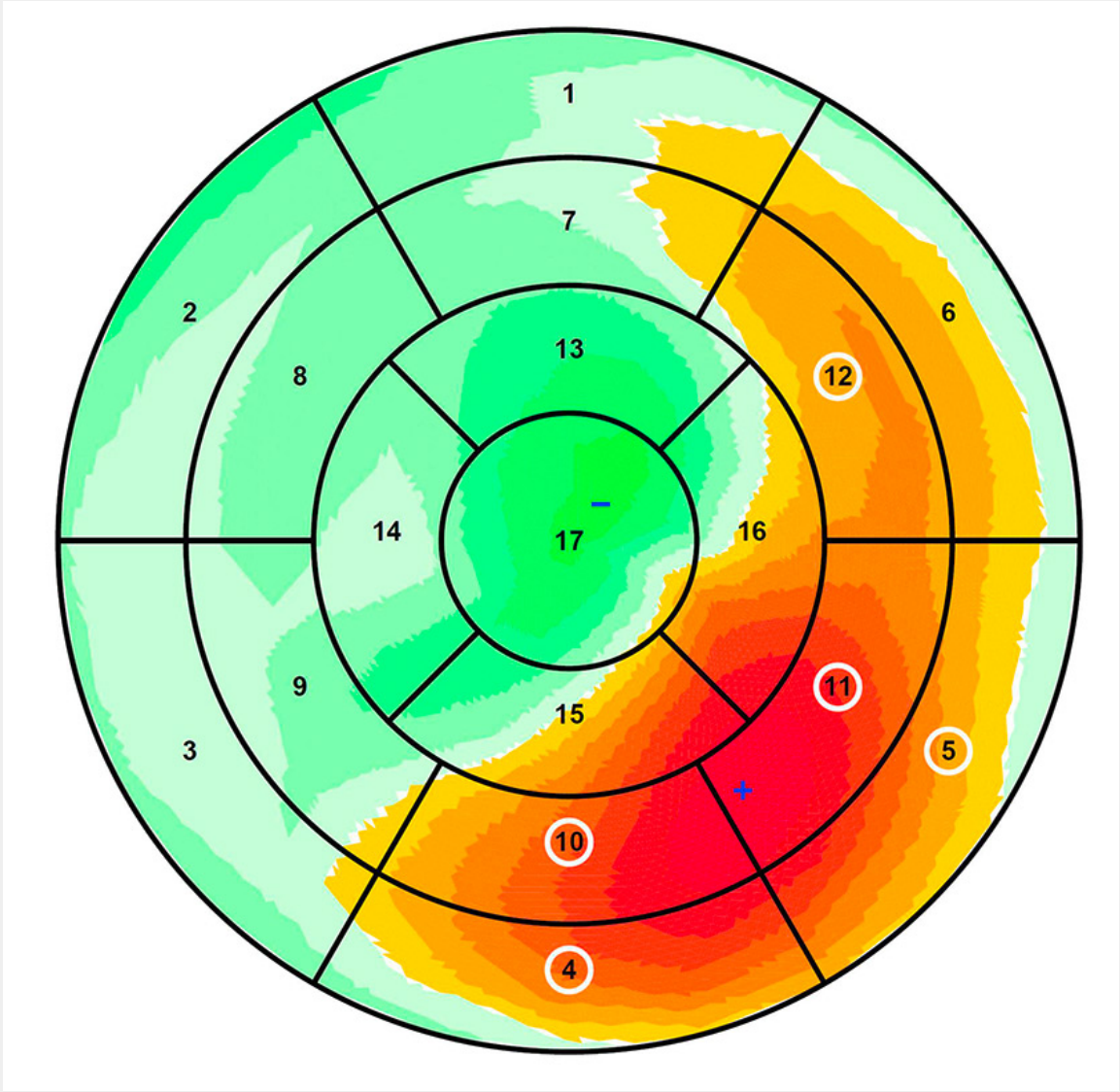

Figure 2

Polarmap of the unipolar epicardial surface potentials obtained at the J-point with ECG imaging in a patient with an left circumflex artery occlusion.

Epicardial unipolar potential distribution obtained from J-point measurements. Yellow to red areas indicate positive potentials and green areas indicate negative potentials. Following the American Heart Association standard 17 segment model, the central part of the image corresponds to the left-ventricular apex and the outermost segments correspond to the basal part of the left ventricular myocardium.

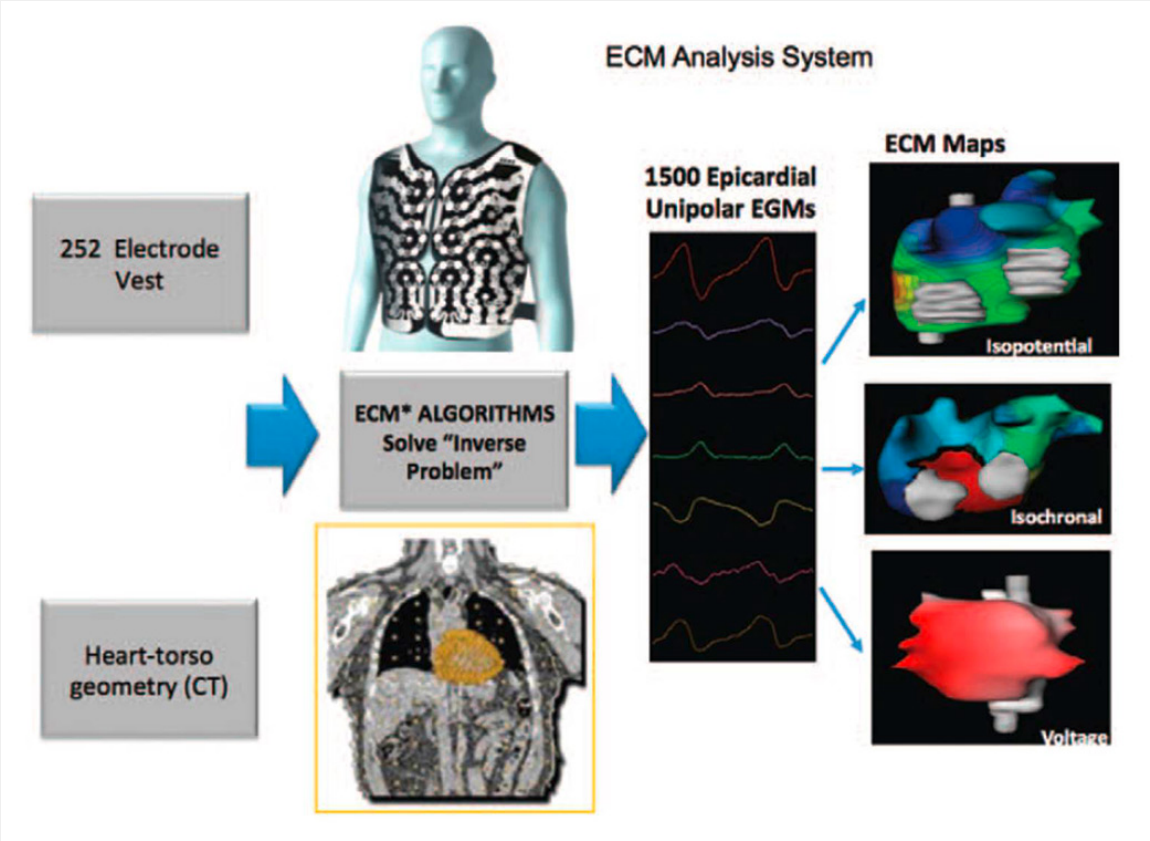

Figure 3

Overview of the components of the ECG mapping system.
The key component of the mapping system is the 252 electrodes that are embedded in a vest that can easily be placed on a patient torso. With the vest on, a computed tomographic (CT) scan of the chest obtains the precise anatomical relation between the 252 electrodes on the vest and the epicardial surface of the heart. Once this anatomic relation is defined, 1500 unipolar electrograms can be calculated from the 252 electrodes using the inverse solution method. Next, isopotential, isochronal, and voltage maps can be reconstructed out of the 1500 unipolar electrograms (reproduced from Cakulev et al. [66] with permission)

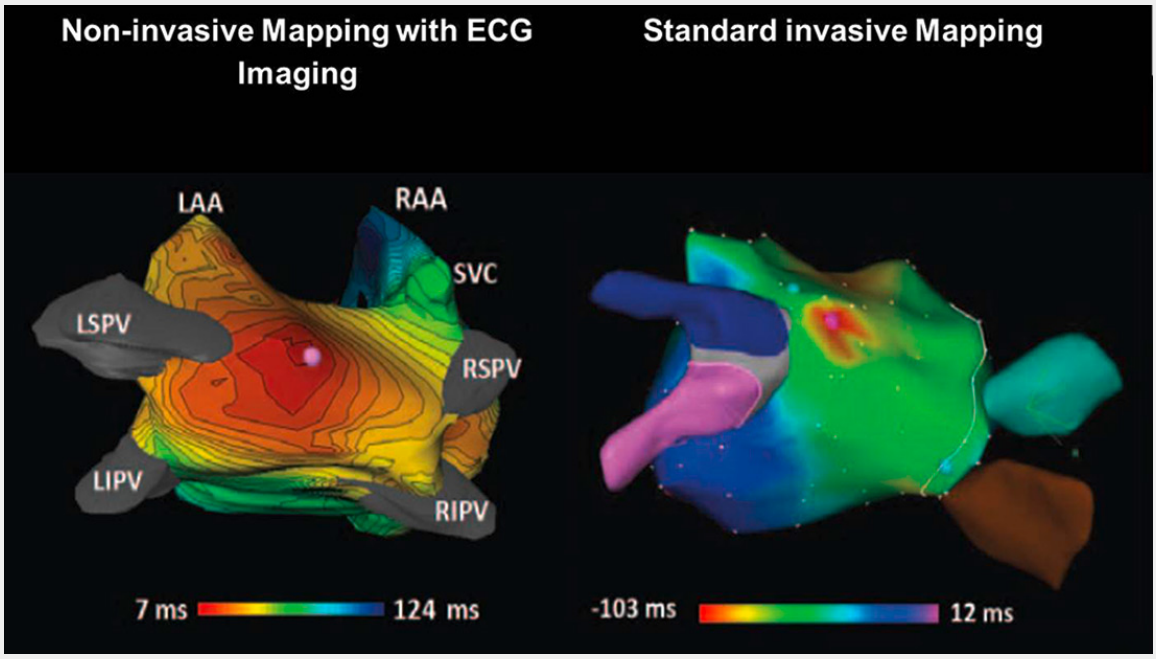

Figure 4

Maps obtained from ECG mapping and standard invasive mapping in a patient with incessant atrial tachycardia.
On the left side of the figure, the map obtained with ECG mapping demonstrated focal activation of the left atrium, with the earliest site of activation on the left atrial roof. On the right side of the figure, the CARTO map with the site of successful ablation that terminated the tachycardia. As can be appreciated, the ECG mapping techniques successfully identified both the tachycardia mechanism as well as the site of earliest activation (reproduced from Cakulev et al. [66] with permission).
LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV =left superior pulmonary vein; RAA = right atrial appendage; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; SVC = superior vena cava